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ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,893	PLOUET ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 8/11/08, is acknowledged.

2. Claim 36 is pending and under examination in the instant application.

3. In view of the amendment filed on 8/11/08, only the following rejections are remained.

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claim 36 stands rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Pat. No. 6,440,733.

The US `733 patent teaches a process for preparing a monoclonal antibody recognizing an antigen on the surface of tumor vessel endothelial cells (an angiogenic phenotype) (col., 4, lines 17-20 in particular), wherein immunization can be accomplished by intraperitoneally administering living cells (10^6 to 10^7 cells) (without adjuvant) as an immunogen. The final immunization involves intravenous administration of 10^6 living cells (see col. 4, lines 42-46 in particular). The `733 patent further teaches that after said immunization, antibody-producing cells for preparing hybridomas are isolated from the immunized animal. Antibody-producing cells are preferably prepared with the spleen extracted from the immunized animal (see col., 5, lines 35-403 in particular). Then, thus obtained antibody-producing cells are immortalized by fusing them to myeloma cells (see col., 5, lines 44-47 in particular) using any cell fusion technique known to those skilled in the art may be used (see col., 5, lines 46-47 in particular). The `733 patent further teaches that the fused cells are selected by cultivation in a HAT medium, the cultivation of cells in the HAT medium may be done for a period enough to kill cells other than hybridomas (see col., 6, lines 3-8 in particular). Further, cell line producing an intended antibody can be subcultured in ordinary media (see col., 6, lines 33-45 in particular). The `733 patent teaches that one of characteristics of monoclonal antibodies of the present invention is that the affinity for tumor vessel endothelial cells is comparable to or Higher than the affinity for normal vessel endothelial cells (see col. 6, lines 64-67 in particular). The `733 patent verifies that the resultant tumor vessel endothelial monoclonal antibodies have antiproliferative effect (angiogenesis-inhibiting properties) on tumor vessel endothelial cells (angiogenic cells) (see Example 5, col., 14 in particular).

The characteristics of the produced antibodies "inhibiting angiogenesis", binds to a surface of the endothelial cells with an angiogenic phenotype" and "recognizes a unit present exclusively on the endothelial cells with an angiogenic phenotype" carry no patentable weight and the claims read on the essential method steps. The recitation of antibody characteristics would not change the property of the produced antibodies nor the way the antibodies is being produced.

Since the office does not have a laboratory to test the reference tumor vessel endothelial cells, it is applicant's burden to show that the reference tumor vessel endothelial cells do not have the properties recited in the claim. Further, See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980). It is noted that tumor endothelial cells are known to be activated by the tumor cell releasing VEGF. Further, VEGF receptors are known to be upregulated on tumor endothelial cells as opposed to endothelial in normal tissue. It is the Examiner's position that the claimed properties are inherent properties to the tumor vessel endothelial cells.

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 8/11/08, have been fully considered, but have not been found convincing.

Applicant submits that neither MAYUMI et al. nor MADRI & WILLIAMS disclose that endothelial need to be cultured with VEGF growth factor. Moreover, regarding the cell culture of endothelial cells (with angiogenic phenotype) this art never mentioned the use of VEGF for their proliferation or for their protection from apoptosis.

However, the claims recites that the endothelial cell "having the following properties", it is the Examiner's position that the referenced tumoral endothelial cells would have the claimed properties. In particular, it is noted that tumor endothelial cells are known to be activated by the tumor cell releasing VEGF. Further, VEGF receptors are known to be upregulated on tumor endothelial cells as opposed to endothelial in normal tissue. It is the Examiner's position that the claimed properties are inherent properties to the tumor vessel endothelial cells. Since the office does not have a laboratory to test the reference tumor vessel endothelial cells, it is applicant's burden to show that the reference tumor vessel endothelial cells do not have the properties recited in the claim. Further, See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

Applicant further argues that regarding the tumoral endothelial cells, they are cultured in a medium formed from calf serum, antibiotics and glutamine. However, MAYUMI et al. (or MADRI & WILLIAMS) never mentioned that said cells are cultured with a supplement of growth factor, and a fortiori supplemented with VEGF.

However, there is no requirement that the endothelial cell be grown on VEGF before injection, the requirement is that the endothelial cell have the claimed properties. It is the examiner's position that the prior art endothelial cells would have the claimed properties.

6. Claim 36 stand rejected under 35 U.S.C. 102(b) as being anticipated by Burrows et al (Clin Cancer Res. 1995 Dec;1(12):1623-34) as is evidenced by Pellizzaro et al (carcinogenesis 23(5):735-740, 2002).

Burrows et al teach the use of subconfluent cultures of HUVECs which had previously been shown to secrete an angiogenic factor as an immunogen to generate monoclonal antibodies. HUVECs were harvested with a rubber policeman and 10^6 cells were injected i.p. into BALB/c mice at 21-day intervals. Fusion with myeloma cells was performed. Hybndoma supernatants (numbering approximately 10,000) were screened for reactivity with proliferating HUVECs. Antibodies that bound to HUVECs in the ELISA were further tested for reactivity with HUVEC cell surface determinants by flow cytometry. Hybridomas secreting antibodies against HUVEC cell surface antigens were cloned and subsequently screened for lack of reactivity with quiescent HUVECs in frozen sections of human umbilical vein. A small panel of antibodies that reacted with proliferating but not with quiescent HUVECs were selected for further immunohistochemical characterization using a series of malignant and normal human tissues. One antibody. TEC- 11. was chosen for further study (see page 1624, under *Production of the TEC-1l Antibody* in particular). Burrows et al teach that increased binding of TEC-11 to tumor vasculature and to dividing as opposed to noncycling HUVECs *in vitro* suggests that endoglin is an endothelial cell proliferation-associated marker. A dgA immunotoxin prepared with TEC-l 1 was greater than 3000-fold more inhibitory to proliferating (verifying angiogenesis-inhibiting properties) *versus* confluent HUVEC cultures (see page 1624, 1st col., 1st full ¶ in particular). Finally, Burrows et al teach that TEC- 11 binding became up-regulated on vessels at approximately the stage at which breast tumors become invasive (new blood vessels formation, angiogenesis) (see page 1627, 2nd col., 1st full ¶ in particular).

While the prior art teachings may be silent as to the "growth factor VEGF" per se; the conditioned medium from a human colorectal carcinoma cell line (HT-29), which had previously been shown to secrete an antigenic factor. The conditioned medium contains high level of VEGF, as evidenced by Pellizzaro et al that VEGF is constitutively expressed at high levels in HT29 (see abstract, page 735 under *VEGF determination by quantitative immunoassay*, Fig. 4). Therefore "inhibiting angiogenic activity" is considered inherent properties.

The characteristics of the produced antibodies "inhibiting angiogenesis", binds to a surface of the endothelial cells with an angiogenic phenotype" and "recognizes a unit present exclusively on the endothelial cells with an angiogenic phenotype" carry no patentable weight and the claims read on the essential method steps. The recitation of antibody characteristics would not change the property of the produced antibodies nor the way the antibodies is being produced.

Since the office does not have a laboratory to test the reference tumor vessel endothelial cells, it is applicant's burden to show that the reference tumor vessel endothelial cells do not have the properties recited in the claim. Further, See In re Best, 195 USPQ 430, 433 (CCPA 1977); In re Marosi, 218 USPQ 289, 292-293 (Fed. Cir. 1983); and In re Fitzgerald et al., 205 USPQ 594 (CCPA 1980).

The reference teachings anticipate the claimed invention.

Applicant's arguments, filed 8/11/08, have been fully considered, but have not been found convincing.

Applicant submits that this art never mentions that endothelial cells (HUVEC) used in this process are **strictly** dependant upon VEGF for their growth and survival. In contrast, the endothelial cells of the present invention are specifically dependent upon VEGF growth factor. This dependency confers specific features such as a high level expression of VEGFR-2 receptor, where claim 36 sets forth that "said endothelial cells expression of VEGFR-2 is increased 4-fold in comparison with cells with a non-angiogenic phenotype."

However, the HT-29 conditioned medium contain the claimed VEGF, the claimed properties are inherent to the referenced endothelial cell. VEGF would induce VEGFR-2 on the referenced endothelial cells in the absence of evidence to the contrary. The term "having" in the claim is open ended it would open up the claim to include other material in addition to "strictly" VEGF.

Applicant submits that the antibodies obtained by the process of the present invention are specific of endothelial cell with angiogenic phenotype, i.e., cells that form tubules in the presence of VEGF when they are cultured in collagen.

It is the Examiner's position that while no specific antibodies are claimed, however that the resultant antibody produce an antibody specific of endothelial cell with angiogenic phenotype, in the absence of evidence to the contrary.

Applicant submits that in contrast, endothelial cells such as HUVEC cells are commonly cultured in endothelial specific culture medium, with or without addition of growth factor. When growth factors are added, a culture medium for the in vitro maintenance of endothelial cells with angiogenic phenotype that contains "Endothelial cell growth supplement (ECGS)" (See ATCC enclosed data sheet of HUVEC - Document i). This "supplement" is known in the art (MACIAG, PNAS, 1979, 76, 5674-78) for containing many growth factors, in particular Fibroblast Growth Factors (FGF-I, FGF2). BURROWS et al. would induce one to provide monoclonal antibody directed against tumoral endothelial cells by immunizing animals with endothelial cells activated by culture medium-secreted growth factors, i.e. mucin, TGFbeta binding protein (See ATCC enclosed data sheet of I-IT9 cells -- Document 2).

Again, the term "having" in the claim is open-ended, it would open up the claim to include unspecific types of growth factors in addition to the VEGF.

Applicant submits that the present invention selects new endothelial cells (dependent upon VEGF for their growth and survival), and these cells are used to produce antibodies specifically inhibiting cells dependent upon VEGF, without affecting properties of endothelial cells without angiogenic phenotype.

Again, these properties are inherent in the prior art method, since the prior art endothelial cells are grown in a medium containing VEGF.

In other words, the antibodies obtained by the process of the invention are not able to inhibits angiogenic properties of endothelial cells non-dependent upon VEGF for their growth and survival (cells disclosed in the cited prior art), but can inhibit cells that are liable to be activated upon VEGF stimulation, or that have been activated by VEGF.

Applicants are arguing limitations that are not claimed.

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claim36 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Pat. No. 6,440,733 in view of US 20020042130 A1.

The teachings of the `733 patent has been discussed, supra. The `733 patent teaches that growing the tumor vessel endothelial cells in DMEM containing endothelial cell growth supplements (see col. 10, lines 12-17 in particular).

The claimed invention differs from the reference teachings only by the recitation of the endothelial cells grow in presence of VEGF.

The `130 publication teaches that the endothelial cell culture medium comprises any of the media conventionally employed for the culture of this type of cell to include an effective amount of endothelial cell growth factor (ECG or VEGF) (¶17 in particular).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the ECGS with VEGF to grow the tumor vessel endothelial cells as taught by the `733 patent.

The claimed endothelial cells properties would be inherent results of the use of VEGF.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because it was conventionally to employ for the culture of endothelial cell any of the media which include an effective amount of endothelial cell growth factor (ECG or VEGF). It conventional to substitute one endothelial cell growth factor with another endothelial cell growth factor as taught by the `130 publication.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

9. No claim is allowed.

10. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B. O'Hara can be reached on (571) 272-0878. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.
Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

October 29, 2008

/Maher M. Haddad/
Primary Examiner
Technology Center 1600